Indian J. Psychiat. (1980). **22**, 176—178

INTRA AND EXTRA ERYTHROCYTE LITHIUM ION CONCENTRATION RATIOS IN MANIC PATIENTS[1]

G. SAMPATH[2], M.D.
B. S. SRIDHARA RAMA RAO, M.Sc., Ph.D., Ph.D.
S. M. CHANNABASAVANNA, M.D., D.P.M.
M. SUBASH, M.Sc.

SUMMARY

In a study RBC-Plasma lithium ratios in manic patients treated with lithium we found that lithium responders had higher lithium ratios than lithium non-responders. There was, however, no cut off value which could differentiate lithium responders from non-responders.

Elizur *et al.* (1972) suggested that erythrocyte lithium to plasma lithium ratio (lithium ratio) may distinguish unipolar from bipolar affective illness. Mendels and Frazer (1973) suggested that lithium ratio may predict response to lithium in depressed patients, in that patients with ratios more than 0.5 would respond to lithium therapy and those with ratios less than 0.5 would not. This was elaborated and corroborated by the same authors in a further study. (Mendels & Frazer, 1974). Cazzulo *et al.* (1975) however found a large number of lithium responders with ratios less than 0.5 among depressives who showed good response to lithium carbonate. Further studies by Lee *et al.* (1975), Carrol (1975) failed to confirm the initial impressions.

All the above studies were done on depressives and as Frazer *et al.* (1978a) point out, these conflicting results could be due to the unipolar-bipolar dichotomy in depressives. They note also, that as a group, the bipolar patients have higher lithium ratios than unipolar.

Frazer *et al.* (1978b) noted that a 300 mg dose of lithium carbonate 2 hrs before sampling for lithium ratios lead to lower values than if the dose were not administered.

We decided to examine lithium ratios in manic patients. Blood samples were taken as a standard 12 hours after the last dose of lithium carbonate, the vagaries in lithium ratio that could occur due to recent ingestion of lithium carbonate could be avoided.

MATERIALS AND METHODS

The study was carried out at the NIMHANS in the period between August 1978 and March 1979. Initially, 35 patients (8 females) were taken for this study, later 2 were dropped for reasons elaborated later. All patients chosen were manic as per criteria of Feighner *et al.* (1972) and care was taken to see that the illness was of sufficient severity to make subsequent judgment on improvement easy. Both the initial choice of patients and subsequent response to lithium were corroborated by 2 psychiatrists, who were not involved in the study. The investigator directly in contact with the patient was blind to the RBC and plasma levels.

After an initial psychiatric assessment and a screening for renal functions (blood urea, serum creatinine, specific gravity, and routine tests for albumin, sugar and microscopy), all patients were treated with lithium carbonate in daily divided doses of 1000—1800 mg so that after a 5 day period, the serum lithium reached 1 mEq/L to 1.4 mEq/L. Serum levels were measured on

[1]Paper presented at the 32nd Annual Conference of Indian Psychiatric Society, Bangalore, 1979 December.
[2]NIMHANS, Bangalore.

the 5th day and also weekly and maintained at 1 mEq/L. If at any time the level was <1 mEq/L the patient was dropped from the study as being irregular on medication (1 patient). In the initial period, patients were on neuroleptic medication in addition to lithium for control of manic symptoms. The dose of the neuroleptic was adjusted as required, but stopped in all patients on 21st day after the serum lithium had attained ≥1 mEq/L. The criteria for response to lithium were :

(1) 21 days after the serum lithium levels had reached 1 mEq/L or more, the patient should not require any additional drugs for maintenance of euthymic state, and
(2) should have normal mental status and sleep for at lasat 72 hrs. after stoppage of medication other than lithium.

One in 3 responders had his lithium stopped ; if he relapsed, but responded again to lithium he was taken as a responder. If he did not relapse, he was considered a spontaneous remitter and was dropped from the study (1 patient, male).

All patients were followed up for 3 months ; the responders were continued on lithium but non-responders were withdrawn from lithium as we did not want a group of "late responders" to emerge and complicate the study.

RBC/Plasma lithium ratios were determined on the 26th day of lithium tretament (21 days after serum lithium reached 1 mEq/L or more.)

Plasma and RBC lithium levels were estimated with 4 ml samples of blood drawn into vials in which previously calculated quantities of Ammonium Heparin were added as anticoagulant. For RBC lithium estimation the method was modified from Pradhan, N. (1978).

The levels and ratios are given in Table 1.

TABLE 1—*RBC/Plasma Lithium Ion Distribution on 26th Day of Lithium Administration*

No.	RBC Li+	Plasma Li+	Li+ Ratio	No.	RBC Li+	Plasma Li+	Li+ Ratio
Lithium Responders							
1.	0.8	1.3	0.62	13.	0.8	1.4	0.57
2.	0.7	1.2	0.58	14.	0.8	1.4	0.57
3.	0.8	1.2	0.67	15.	0.8	1.3	0.63
4.	0.8	1.1	0.73	16.	0.7	1.4	0.50
5.	0.6	1.3	0.46	17.	0.9	1.5	0.60
6.	0.8	1.4	0.57	18.	0.8	1.1	0.73
7.	0.7	1.3	0.54	19.	0.7	1.1	0.64
8.	0.8	1.2	0.58	20.	0.6	1.1	0.55
9.	0.6	1.1	0.55	21.	0.5	1.0	0.50
10.	0.7	1.4	0.50	22.	0.6	1.1	0.55
11.	0.8	1.5	0.53	23.	0.9	1.5	0.60
12.	0.5	1.0	0.50	24.	0.7	1.4	0.50
	..	..	..	25.	0.7	1.2	0.58
Lithium Non-Responders							
1.	0.7	1.4	0.50	5.	0.8	1.6	0.50
2.	0.8	1.5	0.53	6.	0.6	1.4	0.43
3.	0.6	1.3	0.46	7.	0.7	1.4	0.50
4.	0.8	1.4	0.55	8.	0.7	1.2	0.58

Mean Lithium Ratio in Responders=0.574 Variance=0.0046
Mean Litnium ratio in non-Responders=0.5063 Variance=0.0020
t=2.3077 p<0.05

RESULTS

It was found that Lithium ratios were significantly higher in responders ($p<0.05$) than in non-responders. However, there was no cut off point which would help in distinguishing lithium responders from non-responders.

COMMENTS

By taking a group of manic patients, the unipolar-bipolar dichotomy is avoided. Also, by having certain specific criteria for lithium responses, we divided the group into responders and non-responders and removed a possible confounding group of late responders.

The value of lithium ratios are close to those obtained by Flemenbaum *et al.* (1978) and Kim *et al.* (1978) for bipolar depressive. Frazer *et al* (1978b) observed that a group of bipolar affectively ill patients accumulate more intra cellular lithium than others, while we concur with this view (considering mania to be the criteria for bipolar affective illness), we suggest that it is possible that such of those bipolar patients as respond to lithium, tend to accumulate more intra cellular lithium than non-responders. Fraser *et al.* (1978b) had pointed out that standard diagnostic and clinical criteria in studies on lithium ratios were so far not adhered to, but we hope we have satisfied some of them. Also, an attempt has been made to standardize sampling time.

Many reports of possible and proven abnormalities in Lithium transport systems have appeared in recent times. (Ostrov, *et al.* 1978 ; Naylor *et al.*, 1973 ; Fieve, *et al.*, 1978). The implications of our findings in this regard are intriguing.

REFERENCES

Carroll, B. (1975). Lithium Distribution and clinical response. Presented at the Annual meeting of American Psychiatric Association, Anaheim.

Cazzulo, C. L., Smerald, D., Sacchtti, E. and Bottinelli, S. (1975). Intra Cellular Lithium Concentration and Clinical Response. Brit. J. Psychiat., 126, 298.

Elizur, A., Shopsin, B., Gershon, S. and Ehlenberger, A. (1972). Intra Extra Cellular Lithium ratios and clinical course in affective states. Clin. Parmacol. & Ther., 13, 947.

Feighner, J. P., Robins, E. Guze, S. B., Woodruff, R. A., Winokur, G. and Munoz, R. (1972). Diagnostic Criteria for use in psychiatric research. Arch. Gen. Psychiat., 26, 57.

Fieve, R. R., Meltzer, H. L., Dunner, D. L., and Fleiss, J. L. (1978). Lithium Pump repression as an indicator of prophylactic response. Psychopharmacol. Bull., 14, 3, 22.

Flemenbaum, A., Widdige, R., Miller, J. (1978). Lithium Erythrocyte/Plasma Ratio as a Predictor of Response. Amer. J. Psychiat., 135, 3, 336.

Frazer, A., Mendels, J., and Burnswick, D. (1978a) Erythrocyte concentrations of Lithium Ion : Clinical correlates and mechanisms of accumulation. Psychopharmacol. Bull., 14, 3, 14.

Frazer, A., Mendels, J., Burnswick, D., London, J., Pring, M., Ramsey, A., and Rybakowski, J. (1978b). Erythrocyte Concentrations of Lithium Ion : Clinical correlates and mechanisms of accumulation. Amr. J. Psychiat., 135, 9, 1065.

Kim, Y. B., Dunner, D. L., Meltzer, H. L., and Fieve, R. R. (1978). Lithium Erythrocyte Plasma Ratio in Primary Affective Disorder. Comprehensive Psychiat., 19, 2, 129.

Lee, C. R., Hill, S. E., Dimitrakaudi, M., Jenner, F. A., and Pollitt, R. J. (1975). The relationship of plasma to erythrocyte lithium levels in patients taking lithium carbonate Brit. J. Psychiat., 127, 596.

Mendels, J., and Frazer, A. (1973). Intra Cellular Lithium Concentration and clinical response : Towards a membrane theory of depression. J. Psychiat., Res., 10, 9.

Mendels, J., and Frazer, A. (1974). Sodium and Litnium Erythrocyte Concentration in Affective Disorder. J. Psychiat., Res., 10, 157.

Naylor, G. J., Dick, D.A.T., and Dick, E. G. (1973). Erythrocyte Membrane cation carrier in depressive illness. Psychol. Med., 3, 502.

Ostrov, D. G., Pandey, N. G., Davis, J. M., Hurt, S. W., and Toteson, D. C. (1978). A Hereditable disorder of Lithium transport in erythrocytes of a sub-population of manic depressive patients. Amer. J. Psych. 135, 9, 1070.

Pradhan, N. (1978). Validation to the use of RBC as a model for the study of lithium kinetics in affective disorders. MD Thesis, Bangalore, University.